**Updates in Percutaneous Coronary Intervention (PCI)**

**Dr. Kam-tim CHAN**

MBBS, MRCP, FRCP, FHKCP, FHKAM  
Consultant Cardiologist,  
Department of Medicine, Queen Elizabeth Hospital

### Introduction

Ever since the first Percutaneous Coronary Intervention (PCI) with a balloon catheter was performed in 1977 by Dr. Andreas Gruntzig, many significant advances have been made in both the equipment and technology in order to make the PCI procedures more effective and safe. The development of coronary stents, initially bare metal stents and later drug eluted stents, has markedly expanded their clinical applications. However the problems of late stent thrombosis for drug eluted stents have recently aroused much concern in these devices.  

In this article, I shall give a brief summary of some important advances in the field of PCI so as to illustrate our strive to find a better solution for our ischaemic heart diseases patients.

### Assessment of Functional Significance of Stenotic Coronary Lesions

Conventional coronary angiography gives us a luminogram of the coronary artery and is not accurate enough to show the atherosclerotic plaque and its distribution and composition. Intravascular Ultrasound (IVUS) can tell us the exact morphological features of the coronary lesion and with Virtual Histology, the composition of the atheroma can also be clearly identified. The better resolution Optical Coherence Tomography (OCT) technology shows us a better picture of the endoluminal surface and is a great tool in assessing the completeness of endothelialisation of stent struts after implantation. However, all these imaging techniques are not providing information on the physiological significance of these stenotic lesions. Measurement of the Fractional Flow Reserve (FFR) by the Pressure wire can reveal the functional significance of the obstruction and has been proven to be very valuable in guiding intervention. FFR is the ratio of the pressure distal to the obstruction over the pressure at the proximal site during maximal vascular dilatation, and FFR is equal to 1 in normal situation. FFR measurement is independent of changes in blood pressure, heart rate, contractility and takes into account the contribution of the collateral flow. By inducing the state of maximal hyperaemia by giving either intracoronary bolus or intravenous infusion of adenosine, an FFR value < 0.75 means that the obstructing lesion is physiologically significant and requires further intervention.  

The DEFER Trial (Deferral versus performance of PTCA in patients without documented ischaemia) analysed 325 patients scheduled for PCI of an intermediate stenosis. FFR was measured just before the planned intervention. If FFR was ≥ 0.75, patients were randomly assigned to deferral (Defer group; n = 91) or performance (Perform group; n = 90) of PCI. If FFR was < 0.75, PCI was performed as planned (Reference group; n = 144). The five years follow up result of the DEFER trial had shown that the long term outcomes of deferral of PCI of an intermediate coronary stenosis based on FFR ≥ 0.75 was excellent. The risk of cardiac death or myocardial infarction related to this stenosis was < 1% per year and not decreased by stenting.  

The FAME study (Fractional flow reserve vs. Angiography in Multivessel Evaluation) was a prospective randomised multi-centre trial involving 1,005 multivessel diseased patients, aimed to compare the clinical outcomes of PCI guided by conventional angiographic determination of severity or FFR guided therapy. The primary endpoints of the study were death rate, nonfatal myocardial infarction (MI) and Target Vessel Revascularisation (TVR) at one year. There was no differences in the number of intended lesions to be treated per patient (2.7 +/- 0.9 vs 2.8 +/- 1.0; p = 0.34) in the angiogram guided or the FFR guided groups respectively. The FFR guided group received a smaller number of stents (1.9 +/- 1.3 vs 2.7 +/- 1.2; p < 0.001). At 1 year follow up, the composite end point was 13.2 % in the FFR group and 18.3% in the angiogram group (p = 0.02). The FAME trial suggested that by assessing the physiological significance of the stenosis by FFR, the 1 year clinical outcomes of the patients could be improved. Recently, the 2 year data of the FAME trial have been announced and shown that the FFR guided PCI still has a consistently better outcome than the Angiogram guided group.  

For patients with multivessel diseases, it is always difficult to determine which lesion needs to be treated. Revascularisation of lesions producing ischaemia will improve outcomes, but intervention of the stenotic non-ischaemia producing lesions is less clear. Intraprocedural application of the FFR to assess the functional significance of individual lesions will define the optimal revascularisation strategy, and help to improve the clinical outcomes.  

### Percutaneous Coronary Intervention in Acute Myocardial Infarction

The management of patients with acute ST elevation myocardial infarction (STEMI) continues to evolve. The results of the protective devices and rheolytic...
thrombectomy by angioplasty have been proven to be quite unsatisfactory by clinical trials. Although aspiration thrombectomy in these thrombotic situations seems to be intuitive, many previous studies have reported conflicting results. Recently, two clinical trials have yielded more favourable results. The EXPIRA (Impact of Thrombectomy With Export Catheter in Infarct-related Artery on Procedural and Clinical Outcomes in Patients With Acute Myocardial Infarction) trial randomly assigned 175 STEMI patients to conventional primary PCI or aspiration thrombectomy.\textsuperscript{13} The primary endpoints of ST segment resolution and myocardial brush grade ≥ 2 occurred more frequently in the aspiration group, (64% vs 39%; p = 0.0001; 88% vs 60%; p = 0.0001). The thrombectomy group also had a lower mortality rate at 9 months (0% vs 4.6%; p = 0.02).\textsuperscript{14}

The TAPAS trial (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) was a single centre study and randomly assigned 1,071 patients with STEMI to thrombus aspiration or conventional PCI.\textsuperscript{14} At 1 year follow up, cardiac death or reinfarction occurred in 5.6% of patients in the aspiration group and 9.9% of the conventional treatment group (p = 0.009). Although more data are required to routinely recommend aspiration thrombectomy in primary PCI, these two studies support the use of simple aspiration for these high risk patients, especially those with a heavy thrombus burden.

There are convincing data supporting the use of primary PCI for treating STEMI patients. However, when PCI facilities are not available, thrombolytic therapy is still the mainstay of treatment. Recent trials also clearly redefined the role of transferring patients to PCI centres for this effective therapy. The TRANSFER AMI trial (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) randomised 1,059 STEMI patients to receive thrombolytic (tenecteplase; TNK) with subsequent transfer for rescue PCI when required or direct transfer and routine PCI for treating STEMI patients. However, when PCI is not available, thrombolysis therapy is still the mainstay of treatment. Recent trials also clearly redefined the role of transferring patients to PCI centres for this effective therapy. The TRANSFER AMI trial (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) randomised 1,059 STEMI patients to receive thrombolytic (tenecteplase; TNK) with subsequent transfer for rescue PCI when required or direct transfer and routine PCI for treating STEMI patients. However, when PCI is not available, thrombolysis therapy is still the mainstay of treatment. Recent trials also clearly redefined the role of transferring patients to PCI centres for this effective therapy. The TRANSFER AMI trial (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) randomised 1,059 STEMI patients to receive thrombolytic (tenecteplase; TNK) with subsequent transfer for rescue PCI when required or direct transfer and routine PCI within 6 hours for all patients after TNK.\textsuperscript{15} The composite primary endpoints of death, myocardial infarction, recurrent ischaemia, heart failure and shock were lower in the early transfer PCI group (10.5%) than in the standard therapy group (16.5%; p = 0.001). There was similar incidence of major bleeding in both groups (4.3% and 4.6%; p = 0.88). The result of this trial strongly supports that among patients treated with fibrinolysis, routine and early transfer of all patients for adjunctive PCI is superior to a strategy of delayed transfer for rescue PCI in those with failed fibrinolysis.

**Advances in Stent Technology and Platforms**

Despite the proven benefits and efficacy of drug eluted stents, recent concerns have been raised over their long term safety, especially the issue of late stent thrombosis.\textsuperscript{16} The causes of stent thrombosis are multifactorial, attributable to the interplay between patients and lesions factors. The persistence of the stents or the non-absorbable polymers causing inflammation may also be a feasible contributing factor.\textsuperscript{5} Many advances have been made in the area of stent technology, trying to make the next generation stents more efficacious and safer in their application. These include the development of Drug Eluted Stents (DES) with biodegradable polymers, DES that are polymer free, DES with novel stent platforms and coatings and a completely bioresorbable stent.\textsuperscript{16} A complete description of all these new technologies is beyond the scope of this article, however, I would like to elaborate on the certain developments that are considered important in the future management strategies of coronary artery diseases.

**Bioresorbable Stent**

There are currently many long term limitations inherent in the technology of metallic stents. The persistence of the metallic material or the polymer may induce inflammatory response and may contribute to the occurrence of late stent thrombosis. These stented vessels also exhibit impaired endothelial function and render patients unsuitable for subsequent bypass grafting. Other imaging modality like the computerised tomography angiography (CTA) might be difficult to be applied to these stented segments. In order to overcome these problems, a stent that will be entirely resorbed after completing its defined role is a very attractive innovation.

The Abbott Vascular (Santa Clara, CA, USA) fully bioresorbable Vascular Scaffold (BVS) stent has been demonstrated to have a very satisfactory safety profile and clinical outcomes in clinical trials. This new technology is truly an important step forward in the field of PCI. The BVS is made of polyactic acid (PLA), a proven biocompatible material commonly used in medical implants like resorbable sutures. The antiproliferative drug used is Everolimus (Novartis Pharmac.), and is effective in inhibiting the neointimal hyperplasia and smooth muscle cell proliferation. The PLA can be completely metabolised and resorbed by the body and leaves no stent materials inside the artery after 2 to 3 years. The vessels can then resume the ability to flex, contract and pulsate with response to various stimuli, similar to an untreated vessel. (The concept of Vascular Restoration Therapy)

In order to prove its clinical efficacy and safety, the ABSORD trial (a prospective, non-randomised, open label, two phase study) had enrolled 131 patients from New Zealand, Australia and Europe. (30 patients were in the cohort A – the first in men study; the next 101 patients in the cohort B with an improved stent design). The endpoints were the acute results of the BVS, Major Adverse Cardiac Events (MACE) rate and stent thrombosis (ST) rate at 30 days, 6, 9, 12 and 24 months. The patients would be followed up clinically up to five years. Various imaging studies by angiography, Intravascular Ultrasound and Optical Coherence Tomography would be performed at 6, 12, 18, 24 and 36 months. In all the 101 patients, there was no stent thrombosis at 6 month and the MACE rate was 5%.

Two-year follow-up of this first-in-men trial using the BVS Everolimus-Eluting Stent system demonstrated an in-stent late loss of 0.48mm and diameter stenosis of 27%. The two-year OCT and IVUS imaging analysis demonstrated a luminal area enlargement when
compared to 6 months, due to a decrease in plaque burden without any change in vessel size. In addition, vasomotion was restored at the stented site and adjacent coronary artery at 2 years. Clinical outcomes at 3 years have been recently published and it demonstrated a sustained low MACE rate of 3.4% without any late complication of ST.26,27

The ABSORD EXTEND trial is a single arm study that will enroll patients at up to 100 centres in Europe, Latin America, Canada and Asia Pacific regions. It aims to recruit approximately 1,000 patients, including patients with more complex coronary artery diseases. Key endpoints of the study include MACE and stent thrombosis rates at 30 days, 6, 12, 24 and 36 months, as well as an assessment of the acute performance of the bioresorbable vascular scaffold, including successful deployment of the system. This will provide more data on the efficacy and safety of the BVS in a more real-life patient population and better define the potential role of this innovative technology.

Advances in Balloon Technology – the Drug Eluting Balloon (DEB)

Another new advance in the field of interventional cardiology is the development of balloons coated with anti-proliferative drug on the surface. When the balloon is inflated against the arterial wall, the drug will be delivered locally and diffuse directly into the vessel wall to mitigate the restenosis of the artery over time. One of the problems with the use of Drug Eluted Stent is the failure to elute the drug to the entire vessel wall, allowing areas for potential cell growth in areas between the struts. Maximum stent coverage of a vessel wall is around 15-20% only, while on the contrary, the coverage by a DEB is 100%.

The deployment of coronary stents may not be feasible in certain specific lesion subsets like very small vessels with long diffuse diseases, very distal tortuous lesions and small bifurcation lesions. Patients with In-stent restenosis (ISR) of either the drug eluted stents or bare metal stents also pose great challenges for interventional cardiologists. The development of drug eluting balloons (DEB) enables the local delivery of the anti-proliferative drugs directly to the vessel walls and eliminate the potential problems of stenting in small sized vessels. The absence of the rigid stents and the polymers may reduce the chronic inflammation and theoretically decreases the triggers for late stent thrombosis. The good deliverability will allow the DEB to treat those very tortuous, distal and small diffusely diseased vessels. It is also a good tool to deal with the problems of ISR, where additional stent in stent strategy will increase the metal load, has higher chance of restenosis again and stent thrombosis. The absence of the stent struts and local drug delivery also diminish the need for prolonged dual anti-platelet therapy. However, DEB is still unable to overcome the problem of acute elastic recoil after any simple balloon angioplasty. The combination of a DEB with a bare metal stent (BMS) may seem to be a viable option.

The most commonly used agent is paclitaxel, which is rapidly absorbed by the vascular smooth muscle cells and is retained inside the tissue for one week to exert a prolonged antiproliferative effect.28,29 There are several devices currently available in our locality. (SeQuent Please DEB -by B. Braun; DIOR DEB – by Eurocor; In.PACT Falcon DEB – by Invatec)

Currently, many clinical trials are being performed to analyse the safety and efficacy of DEB in the treatment of ISR, de novo lesions and bifurcation lesions.30–35

DEB for treating In-stent Restenosis (ISR)

Scheller et al. published the results of the PACCOCATH ISR I (Paclitaxel-Coated Balloon Catheter for In-stent Restenosis ) in 2006.36 The trial randomised 52 patients with ISR of a single lesion to either standard balloon angioplasty or paclitaxel-coated DEB. The primary endpoint of in-segment lumen loss was significantly lower in the DEB group (0.03 +/- 0.48mm vs. 0.74 +/- 0.86mm, p= 0.002). The DEB group also had significantly lower binary restenosis and MACE rates. The PEPCAD II (Paclitaxel – Eluting PTCBalloon Catheter in Coronary Artery Diseases) multicentre study involved 131 patients with ISR, and were randomised to treatment with the SeQuent Please DEB (B. Braun) or the TAXUS stent (Boston Scientific).37 At 6 month follow up, the in-segment late loss was again significantly lower in the DEB group, (0.17 +/- 0.42 mm vs 0.38 +/- 0.61 mm; p= 0.03) which also demonstrated a trend of lower binary restenosis rate (7% vs 20%; p= 0.06). At 12 month follow up, the MACE rates for the DEB and Taxus group were 9% and 22% respectively (p= 0.08), which was largely driven by the higher Target Lesion Revascularization (TLR) rate in the Taxus patients (6% vs 15 %; p= 0.15). Overall, these studies have shown that the DEB was safe and at least as effective as Taxus in treating patients with ISR.

DEB for de novo lesions :

The role of DEB in treating de novo lesions is less well defined as compared with the ISR management. Many studies have yield inconsistent results. The PEPCAD I multi-centre prospective registry analysed 120 patients with de novo lesions and a reference vessel diameter of 2.25mm to 2.8 mm.36,37 There was a high proportion of patients (1/3) requiring stenting with a bare metal stent (BMS) after DEB due to unsatisfactory balloon results. At 6 month follow up, the late lumen loss was 0.18 mm for the DEB group, while patients with DEB and BMS had a late loss of 0.73mm. Similarly, the binary restenosis rates were 5.5% and 44.8 % respectively. The combination therapy of DEB with BMS has yielded the high restenosis rate which is quite unacceptable by the current standard.

The PEPCAD III was an non-inferiority study, and tended to compare the Cypher Sirolimus Eluting Stent (SES, Johnson and Johnson) with the Coroflex DEBlue (BMS/ DEB combination; B. Braun) in 637 patients with stable or unstable angina.34 At 9 month follow up, the instant late lumen loss (0.16 mm vs 0.41 mm; p < 0.001) and ISR (2.9% vs 10%; p < 0.01) were both significantly lower in the SES group as compared with the BMS/ DEB arm. The total mortality was comparable in both arms, but the BMS/ DEB arm had a significantly higher MACE rates of MI, TLR, TVR and stent thrombosis (p < 0.05 for all).

In the PICCOLETO trial (Paclitaxel–Eluting Balloon
versus Paclitaxel–Eluting Stent in Small Coronary Artery Diseases), 57 patients with stable or unstable angina and small vessels (≤ 2.75mm) were randomised to receive the DIOR DEB (Eurocor) or Paclitaxel-Eluting stents. (PES). The DEB arm had a higher percentage diameter stenosis (43.6 +/- 27.4% vs 24.3 +/- 25.1%; p = 0.029 ) when compared with the PES group at 6 month follow up. The binary restenosis rate and minimal lumen diameter were also significantly worse with the DEB and there was a trend of higher TLK in the DEB group.

In summary, the initial results of DEB are quite promising in specific patients and lesions subset, especially those with ISR. We definitely require more researches in the future to elucidate the more specific role of DEB in other patient populations.

Update on Antiplatelet Agents for PCI

It is of vital importance to prescribe dual anti-platelet therapy (DAPT) of aspirin and clopidogrel after stent implantation to prevent the disastrous complication of stent thrombosis. The patients are recommended to take at least 1 month DAPT for bare metal stents and 12 months after drug eluted stents implantation. Clopidogrel is a pro-drug and requires the active metabolism by a liver enzyme, CYP2C19, for conversion to the active form to exert its anti-platelet activity. Several different alleles of CYP2C19 have been identified in the population. Depending on the alleles carried, patients may demonstrate normal, reduced or increased activity of CYP2C19. The *1 allele is the normal allele and has full enzymatic activity. The *2 and *3 alleles are the most common variants and result in complete loss of enzymatic activity. Patients carrying these two alleles have reduced clopidogrel–induced anti-platelet activity. The prevalence of *2 and *3 alleles varies with different racial backgrounds. The proportion of patients with *2 alleles is estimated to be 25%, 30% and 40-50% in Caucasians, Blacks and Asians respectively.

Nowadays, there are laboratory tests available for checking the platelet reactivity and the Cytochrome CYP2C19 genotypes variation for patients taking the anti-platelet agents. However, there are currently no recommendations or guidelines on the use of genetic tests to monitor the anti-platelet therapy. Moreover, the effects on the cardiovascular outcomes by the number of variants carried by the patients have not been clarified yet. The US Food and Drug Administration has recently issued a boxed warning to clopidogrel, stating that, in certain patients with a genetic variation of the enzyme CYP2C19, the drug may not be metabolised properly and may not be effective for its anti-platelet activity. For these patients, a higher dose of clopidogrel (600 mg loading dose followed by 150 mg daily maintenance dose) or an alternative anti-platelet medication such as prasugrel, may be indicated. Despite these possible remedial action to increase the anti-platelet response in those poor responders, an appropriate dose regimen has not yet been established in a clinical outcome trial. Undoubtedly, we need more large scale randomised controlled trials to give us more definitive answer to these questions.

Conclusion

In the last 30 years, there have been very significant advances made in the field of PCI. Development of new devices and technology will enable the patients to be treated with improved long term efficacy and safety. Our strive for excellence and continuous improvement will never stop and the next generation devices will overcome the limitations of old technology and markedly expand the application of PCI in our day to day practices.

References


